

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/007762 A3

(51) International Patent Classification⁷: **C12Q 1/68**

79618 Rheinfelden-Herten (DE). **KOENIG, James, Irvin**
[US/US]; 1406 Tuffed Moss Court, Crofton, MD 21114
(US).

(21) International Application Number:
PCT/EP2003/007491

(22) International Filing Date: 10 July 2003 (10.07.2003)

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/395,088 11 July 2002 (11.07.2002) US
60/472,489 22 May 2003 (22.05.2003) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except AT, US*): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

(71) Applicant (*for AT only*): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

Published:

— with international search report

(71) Applicant (*for all designated States except US*): **UNIVERSITY OF MARYLAND** [US/US]; 520 West Lombard Street, Baltimore, MD 21201 (US).

(88) Date of publication of the international search report:
27 May 2004

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BILBE, Graeme** [GB/CH]; Chemin de Maujobia 37, CH-2000 Neuchâtel (CH). **KINNUNEN, Anu** [FI/DE]; Kirchstrasse 11,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GENES ASSOCIATED WITH SCHIZOPHRENIA, ADHD AND BIPOLAR DISORDERS

(57) Abstract: Disclosed are methods for diagnosing, monitoring the progression of, and treating schizophrenia, bipolar disorder, and/or ADHD based upon genes that are differentially expressed in said disorders at baseline, or at different timepoints following an acute stress exposure. Also disclosed are methods for identifying agents useful in the treatment of schizophrenia, bipolar disorder, and/or ADHD, methods for monitoring the efficacy of a treatment for schizophrenia, bipolar disorder, and/or ADHD, methods for preventing and treating schizophrenia, bipolar disorder, and/or ADHD, and an animal model for schizophrenia, bipolar disorder, and/or ADHD.



WO 2004/007762 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/07491

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DUGOVIC C ET AL: "High corticosterone levels in prenatally stressed rats predict persistent paradoxical sleep alterations" JOURNAL OF NEUROSCIENCE, vol. 19, no. 19, 1 October 1999 (1999-10-01), pages 8656-8664, XP002259919 ISSN: 0270-6474 abstract page 8656 - page 8657 ----- -/--	26

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

31 October 2003

Date of mailing of the international search report

30.12.2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

van Klompenburg, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/07491

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KANG I ET AL: "PERSISTENT ELEVATION IN GABA-A RECEPTOR SUBUNIT MESSENGER RNAS FOLLOWING SOCIAL STRESS" BRAIN RESEARCH BULLETIN, vol. 26, no. 5, 1991, pages 809-812, XP008023743 ISSN: 0361-9230 figure 2A	1-16, 21-26
A	YMER S ET AL: "STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF THE GAMMA-1 SUBUNIT OF GABA-A BENZODIAZEPINE RECEPTORS" EMBO JOURNAL, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 9, no. 10, 1990, pages 3261-3268, XP002199264 ISSN: 0261-4189 figure 1; table 1	1-16, 21-26
A	COSTA ERMINIO: "Building a bridge between neurobiology and mental illness" JOURNAL OF PSYCHIATRIC RESEARCH, vol. 26, no. 4, 1992, pages 449-460, XP008023742 International Workshop on Genetics and Gene Expression in Mental Illness; Venice, Italy; October 28-31, 1991 ISSN: 0022-3956 page 457	1-16, 21-26
A	EP 1 132 483 A (PRESIDENT OF NIIGATA UNIVERSIT) 12 September 2001 (2001-09-12) page 2 - page 6; claims 1-3	1-16, 21-26
A	WO 01/075440 A (COCHRAN SUSAN ; PATERSON GARY (GB); MORRIS BRIAN (GB); PRATT JUDITH) 11 October 2001 (2001-10-11) claims 1-45; examples 1,3,4	1,16, 21-26
T	KINNUNEN A K ET AL: "Repeated variable prenatal stress alters pre- and postsynaptic gene expression in the rat frontal pole" JOURNAL OF NEUROCHEMISTRY 2003 UNITED KINGDOM, vol. 86, no. 3, 2003, pages 736-748, XP002259821 ISSN: 0022-3042 the whole document	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07491

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-12 are directed to a diagnostic method practised on the human/animal body, the search has been carried out on the in vitro steps of the diagnostic method.
2. ☒ Claims Nos.: 17-20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-16, 21-25 all partially as far as applicable, 26 completely

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17-20

Present claims 17-20 relate to a compound defined by reference to a desirable characteristic or property, namely the ability to induce a decrease or increase in the expression of a gene of interest

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 17-20.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-16,21-25 all partially as far as applicable, 26 completely

A method for screening a subject for schizophrenia, bipolar disorder and/or ADHD or at risk of developing schizophrenia, bipolar disorder and/or ADHD, the method comprising: a) detecting a level of expression of the gene with accession number X57514 from the subject; b) comparing the level of expression of X57514 with that of a disease-free subject.

A method for monitoring the progression of schizophrenia, bipolar disorder and/or ADHD in a subject having or at a risk of having said disorders.

A method for identifying agents for use in treatment of schizophrenia, bipolar disorder and/or ADHD.

A method for monitoring the efficacy of a treatment of a subject having schizophrenia, bipolar disorder and/or ADHD.

A transgenic mouse for whose genome comprises a disruption of the endogenous gene X57514

A method for producing a rodent having schizophrenia, bipolar disorder and/or ADHD.

Inventions 2-29: claims 1-16,21-25 all partially and all as far as applicable.

As invention 1, but without the method to produce a rodent having schizophrenia, bipolar disorder or ADHD, and where invention 2 is characterized by the gene with accession number U66707, invention 3 by AI639165, 4 by AF064868, 5 by AI145494, 6 by U20643, 7 by H31232, 8 by S61973, 9 by AB016160, 10 by X85184, 11 by J04063, 12 by S81353, 13 by S81353, 14 by M33025, 14 by AA858621, 15 by M74494, 16 by AA866358, 17 by M64986, 18 by AI227715, 19 by U77931, 20 by AA89392, 21 by AA859633, 22 by AA891969, 23 by AI145367, 24 by AA893711, 25 by Y09000, 26 by AA891940, 27 by D26564, 28 by AI101103, 29 by AF014009,

Inventions 30-95: claims 1-16,21-25 all partially and all as far as

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

applicable.

As invention 2, but where invention 30 is characterized by the gene with accession number AA946532, 31 by AB016160, 32 by U57500, 33 by L17127, 34 by M28648, 35 by L24776, 36 by AB020504, 37 by U77931, 38 by U75927, 39 by AF096269, 40 by AA892801, 41 by U49099, 42 by AA859597, 43 by AA875427, 44 by AF028784, 45 by L22760, 46 by AI014135, 47 by AI104513, 48 by AA8944148, 49 by AI073204, 50 by D38468, 51 by M13100, 52 by M59980, 53 by M18331, 54 by M36418, 55 by X57764, 56 by U62897, 57 by S71570, 58 by M16112, 59 by AI008131, 60 by X12744, 61 by AI230260, 62 by U48245, 63 by U66707, 64 by H31692, 65 by D89863, 66 by X06564, 67 by M91234, 68 by U31554, 69 by AA875659, 70 by AA799421, 71 by AI014091, 72 by AB012234, 73 by U09793, 74 by AA800513, 75 by AI639381, 76 by AA799515, 77 by X83546, 78 by AI013194, 79 by AB008538, 80 by X52817, 81 by AA893065, 82 by H31588, 83 by AA859832, 84 by AI00874, 85 AA851749, 86 by AA894321, 87 by AI227608, 88 by E13644, 89 by AA925762, 90 by M72422, 91 by M17526, 92 by U45479, 93 by U86635, 94 by AA894089, 95 by AA891069

Inventions 96-160: claims 1-16,21-25 all partially and all as far as applicable.

As invention 2, but where invention 96 is characterized by the gene with accession number U66707, 97 by AA900582, 98 by AI012942, 99 by AF04868, 100 by AI044716, 101 by AF068136, 102 by X58865, 103 by AI179150, 104 by AA800881, 105 by K02248, 106 by AF001423, 107 by AI639157, 108 by AA891901, 109 by M30691, 110 by AI234950, 111 by X57514, 112 by S79523, 113 by AI639165, 114 by D00913, 115 by AJ224680, 116 by AA893711, 117 by AI639422, 117 by D14015, 118 by L31840, 119 by AF087674, 120 by X05472, 121 by AI145494, 122 by U77583, 123 by AA892797, 124 by U70268, 125 by M88751, 126 by AA892376, 127 by AA866459, 128 by AA892483, 129 by AA891969, 130 by AJ001641, 131 by AA799636, 132 by AA94054, 133 by AI008131, 134 by AA893670, 135 by AI22715, 136 by AA799576, 137 by AA799791, 138 by AA874982, 139 by X76489cds, 140 by Y09000, 141 by AA859663, 142 by U77931, 143 by AI145367, 144 by D10666, 145 by D38560, 146 by AB003992, 147 by AA859520, 148 by AB003991, 149 by AA894264, 150 by AA955388, 151 by X07729, 152 by M62752, 153 by AA799479, 154 by H32977, 155 by X54531, 156 by M64986, 157 by AA893164, 158 by M35300, 159 by AB016160, 160 by AI101103

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07491

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1132483	A	12-09-2001	JP 2001245661 A	11-09-2001
			EP 1132483 A2	12-09-2001
			US 2003157548 A1	21-08-2003

WO 0175440	A	11-10-2001	AU 4435801 A	15-10-2001
			EP 1356284 A2	29-10-2003
			WO 0175440 A2	11-10-2001
			JP 2003531587 T	28-10-2003
			US 2003175741 A1	18-09-2003
